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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/420,433	10/12/1999	DAVID SIDRANSKY	JHU1180-1	2810

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Lisa A. Haile
Gray Cary Ware & Freidenrich LLP
4365 Executive Drive
SUITE 1100
San Diego, CA 92121-2133

EXAMINER	
JOHANNSEN, DIANA B	

ART UNIT	PAPER NUMBER
1634	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	09/420,433	SIDRANSKY, DAVID	
	Examiner	Art Unit	
	Diana B. Johannsen	1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *10 April 2008*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-4,7-12,14,18-22 and 24-26* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-4,7-12,14,18-22 and 24-26* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

FINAL ACTION

1. This action is responsive to Amendment and Response filed April 10, 2008. Claims 1-3, 11-12, 18-21, and 25-26 have been amended. Claims 1-4, 7-12, 14, 18-22, and 24-26 are now pending and under consideration. Applicant's amendments and arguments have been thoroughly reviewed, but are not persuasive for the reasons that follow. Any rejections and/or objections not reiterated in this action have been withdrawn. **This action is FINAL.**

2. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Claim Rejections - 35 USC § 112

3. Claims 1-4, 7-12, 14, 18-22, and 24-26 remain rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention, for the reasons set forth in the prior Office action of December 13, 2007, which reasons are reiterated below.

There are many factors to be considered when determining whether there is sufficient evidence to support a determination that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is "undue." These factors include, but are not limited to: (A) the breadth of the claims; (B) the nature of the invention; (C) the state of the prior art; (D) the level of one of ordinary skill; (E) the level of predictability in the art; (F) the amount of direction provided by the inventor; (G) the

existence of working examples; and (H) the quantity of experimentation needed to make or use the invention based on the content of the disclosure. *In re Wands*, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988) (*MPEP* 2164.01(a)).

Claims 1-4 and 7-11 are drawn to methods in which a "target neoplastic nucleic acid" selected from APC, DCC, NF1, NF2, RET, VHL, and WT-1 is detected in a tumor margin tissue specimen that is "external to a primary neoplasm" and "histologically normal." Claims 12 and 14 are drawn to methods in which a "target neoplastic nucleic acid" that is selected from APC, DCC, NF1, NF2, RET, VHL, and WT-1 is detected in a surgical margin that is "histologically normal" as an indicator of metastases. Claim 18 encompasses detection of such a target neoplastic nucleic acid in a "tissue specimen which is external to a primary neoplasm" and "histologically normal," while claim 19 requires the presence of such a nucleic acid in a "tumor margin tissue specimen" that "appears histologically normal." Claims 20-22 and 24 are drawn to methods in which a "target neoplastic nucleic acid" selected from APC, DCC, NF1, NF2, RET, VHL, and WT-1 is detected in a "lymph node tissue specimen" that is "external to a primary neoplasm" and which "appears histologically normal." Claims 25-26 are drawn to methods in which a "target neoplastic nucleic acid" that is selected from APC, DCC, NF1, NF2, RET, VHL, and WT-1 is detected in tissue from a lymph node that is "external to a primary neoplasm" and "appears histologically normal" as an indicator of metastases.

It is unpredictable as to whether one of skill in the relevant art could use the invention of the instant claims. The claims as written require that each of the "target

neoplastic" nucleic acids recited therein may be detected in tumor margins and lymph node tissues that are or appear "histologically normal." However, the specification only exemplifies the detection of a different target nucleic acid, p53, in surgical margins and lymph nodes that appear histologically normal by light microscopy in patients afflicted with head and neck squamous cell carcinoma (see Examples 1-4, as well as Figures 2-5 and 7-9). Applicant's specification does not provide any evidence that mutated versions of any of the nucleic acids recited in the instant claims were -- or can be -- detected in any type of sample (from any type of patient, with any type of cancer) that is or that appears "histologically normal." Many types of microscopy were available for use by those of skill in the art at the time the invention was made, and additional techniques such as staining and labeling may be employed with microscopy to increase its sensitivity. Given the absence of evidence and data provided in the specification regarding the detection of the nucleic acids of the claims in any type of "histologically normal' sample, it is completely unpredictable as to whether said nucleic acids may in fact be detected by the methods of the claims in such samples. With further regard to claims 12 and 25 and claims dependent therefrom, it is further noted that the specification is also silent with regard to detection of any of these nucleic acids in any type of "histologically normal' sample as an indicator of metastasis. Lacking guidance from the specification, one of skill in the art may look to the teachings of the art for further guidance and enablement of a claimed invention. However, in the instant case, the prior art is also silent with respect to any teachings that mutant versions of any of the genes of the instant claims may be detected in, e.g., surgical margins or lymph

nodes that are or appear "histologically normal." The closest prior art reference, Nees et al (Cancer Research 53(18):4189-4196 [9/1993]), discloses that mutated p53 nucleic acids were detected in tumor margin specimens obtained from patients with head and neck cancers (see, e.g., Table 3, p. 4191, 4193). However, Nees et al note that their findings with p53 suggest that multiple tumor development may be a "multifocal polyclonal process" rather than a monoclonal process "initiated by lateral movement" of premalignant cells, and state that "At present, there is no information as to which other tumor suppressor genes" might be among those that (along with p53) undergo genetic changes contributing to head and neck cancer progression (see page 4195, last paragraph). Thus, the teachings of the prior art suggest the manner in which cells containing the mutant nucleic acids of the claims might arise in lymph nodes and/or tumor margin tissues is not clear. Further, the teachings of the specification also support a conclusion that p53 is not analogous or equivalent to the genes of the present claims; for example, page 11 of the specification teaches that p53 mutations are found in "50% of all cancers," while showing that the genes of the present claims are associated with particular cancer types.

Given the lack of evidence in both the specification and in the art with regard to how (or even whether) cells comprising the nucleic acids of the claims might spread to lymph nodes and/or tumor margin tissues, it cannot be predicted whether specimens taken from these locations that were found to contain detectable levels of such "target neoplastic" nucleic acids would in fact appear histologically normal. As noted above, many types of microscopy were available for use by those of skill in the art at the time

the invention was made, and additional techniques such as staining and labeling may be employed with microscopy to increase its sensitivity. While it is certainly possible that such specimens might be identified, this question could only be resolved by further experimentation. Given the high level of skill of one skilled in the relevant art, it is clearly within the ability of such an artisan to conduct such further experimentation – however, the outcome cannot be predicted, and it is in fact possible that no quantity of experimentation would be sufficient to enable the claims. As it is unknown as to whether any quantity of experimentation would actually be sufficient to enable the practice of the claimed invention, it would clearly require an undue quantity of experimentation to use the invention of the instant claims.

The response of April 10, 2008 traverses the rejection on the following grounds.

First, the reply argues that the specification "provides abundant guidance for the practice of the claimed methods as well as a detailed working example," and that a skilled artisan "would have reasonably expected that mutations….which are found in the primary tumor, could similarly be detected in normal-appearing tissues into which tumor cells from the primary tumor had migrated." The reply urges that "the skilled artisan simply need know whether one or more of the target neoplastic nucleic acids is present in a mutated form in the primary neoplasm," and that "as it is known in art" that the genes of the claims "and mutated forms thereof have been associated with specific cancer types," a skilled artisan "can readily assay the neoplasm and a histologically normal tissue specimen for the mutant nucleotide sequence of the relevant tumor

suppressor gene using the methods exemplified for p53." These arguments have been thoroughly considered but are not persuasive. It is again noted that the specification only exemplifies the actual practice of methods of the type encompassed by the claims with p53 (not with any of the genes of the present claims). Neither the teachings of the prior art nor those of the specification have established that p53 is analogous to the genes of the instant claims, and it is again noted that applicant's own specification discloses that p53 is associated with a wide variety of cancers while the genes of the claims are associated only with particular cancer types, emphasizing the differences that exist between p53 and the genes of the instant claims. Further, neither the specification nor the prior art provide any actual evidence that any of the genes encompassed by the instant claims had been or could be successfully detected in "histologically normal" samples at the time the instant invention was made (which is the date relevant to enablement of a claimed invention). The examiner has not disputed the fact that one could have successfully attempted such diagnostic techniques on histologically normal tissues using techniques known in the art and taught in the specification; however, enablement of the instant claims requires actual detection, not attempted detection.

The reply further argues that the post-filing date references of Wang et al (published approximately 10 years after the effective filing date of the instant application) and Bilchik et al (published approximately 7 years after the effective filing date of the instant application) support the operability of the claimed invention. However, neither of these references provide evidence that the methods of the instant

claims were enabled as of applicant's effective filing date (which is the date relevant to enablement). It is first noted that the Wang et al reference is limited to findings obtained with serum samples. A skilled artisan would recognize that serum, which is a clear, cell-free substance obtained following the clotting of blood, is not in fact a tissue, and could not even be evaluated with respect to tissue histology, as is required by the instant claims. Thus, Wang et al's post-filing date findings using serum have no bearing on the enablement of the claimed invention. The examiner concurs that the Bilchik et al references establishes that, as of 2001, a skilled artisan could detect colorectal cancer micrometastases by RT-PCR detection of 3 markers known to be overexpressed in such cancers. However, the markers detected by Bilchik et al differ from those of the claims, and have not been established as being in any way analogous to the genes of the instant claims. Further, the teachings of Bilchik et al reported in 2001 do not in any way establish that the invention of the instant claims was enabled in 1994, and it is further noted that Bilchik et al teach that because different sections are employed for RT-PCR and histopathological analysis, tumor cells may be present in one place and not in the other (page 1134, left column); thus, a skilled artisan would recognize that a single sample may include areas including tumor cells and areas lacking tumor cells, such that different findings may be obtained using the same sample. It is again noted that applicant's specification does not establish that any of the genes of the claims have been successfully detected in any sample appearing "histologically normal." Finally, with regard to applicant's arguments pertaining to different types of microscopy, it is again noted that the instant rejection stems from the fact that applicants have simply not

established (via the specification or any other arguments or evidence) that, as of the time the instant invention was made, any of the genes of the claims had been or could be detected in any "histologically normal" sample. Applicant's arguments have been thoroughly considered but are not persuasive. This rejection is maintained.

Conclusion

4. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Diana B. Johannsen whose telephone number is 571/272-0744. The examiner can normally be reached on Monday through Friday, 7:30 am-4:00 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ram Shukla can be reached at 571/272-0735. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Diana B. Johannsen/
Primary Examiner, Art Unit 1634

Diana B. Johannsen
Primary Examiner
Art Unit 1634